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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,632	04/07/1999	PETER MICHAEL WATERHOUSE	021565-060	6526

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/09/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/287,632	WATERHOUSE ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,22,25,26,40,42-44,46-54,56 and 58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,22,25,26,40,42-44,46-54,56 and 58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The rejections of record under 35 USC 112, first and second paragraph, set forth in the prior Office action, mailed July 16, 2002, have been withdrawn in response to Applicant's amendments and arguments filed January 16, 2003. However, new grounds of rejection are set forth herein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22, 42, 53, 54, 56 and 58 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 22, 42, 53, 54, 56 and 58 are directed to eukaryotic cells, wherein the cells comprise a particular transcribed DNA. The claims, however, would encompass eukaryotic cells comprising the transcribed DNA existing in a whole organism, including a person, and therefore, is considered to be non-statutory. Amending the claims to indicate the cell is isolated would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 22, 25, 26, 40, 42-44, 46-48, 50-54, 56, and 58-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 22 recite the limitation "heterologous intron sequence", however, it is unclear what the intron sequence is heterologous to, for example, is it heterologous to the eukaryotic cell, the target gene, the transcribed DNA, or perhaps something else? The metes and bounds of the claims are unclear, because it is unclear what the intron sequence is heterologous to. Claims 3-21, 25, 26, 40, 42-44, 47, 50, 51, 53, 54, 58, 59, and 61 are indefinite for the same reasons due to dependence on either claim 1, 2 or 22.

Claims 46, 48, 52, 60 and 62 are indefinite because they depend upon a canceled claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 40, 43, 44, 50, and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the phenotypic expression of a nucleic acid of interest using a transcribed dsRNA in a eukaryotic cell in vitro or in a plant, does not reasonably provide enablement for methods of reducing the phenotypic expression of a nucleic acid of interest using a

transcribed dsRNA in a eukaryotic cell in vivo (whole organism) in generally any eukaryotic organism, particularly in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-10, 40, 43, 44, 50, and 51 are drawn broadly to methods of reducing the phenotypic expression of a nucleic acid of interest in a eukaryotic cell in any setting, in vitro or in vivo (whole organism), for any organism, including humans and other mammals, using a DNA administered to the cell wherein the DNA expressed a dsRNA. The claimed methods read on gene therapy and would encompass methods wherein the expression of a nucleic acid is reduced and a phenotypic result is provided in vivo, including for therapeutic purposes.

The specification provides examples wherein the phenotypic expression of target nucleic acids, including viral nucleic acids, are reduced in transgenic plants using an expressed dsRNA. The specification does not provide any examples wherein their claimed methods are used to reduce the phenotypic expression of a target nucleic acid in a mammal, including humans, or any organism besides plants.

Methods of inhibiting gene expression using nucleic acids in vivo (whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, including, for example, a reduction in a particular phenotype, as claimed. In the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene, as gene therapy methods (i.e. nucleic acids expressed from a vector) are further hampered by unpredictable loss of expression (see for example Anderson, W.F. and Verma et al.). Verma et al. and Anderson do not make reference to DNA vector that express a dsRNA, as claimed, however, the methods claimed require that a vector expressing an RNA be delivered specifically to a target cell in an organism in vivo (whole organism) at a concentration effective enough to inhibit the expression of a target gene and at a concentration effective enough to inhibit the expression of a gene to the extent that the organism exhibits a phenotype reflecting the inhibition of expression. At the time of the filing of the instant application, and even to date, in vivo systems for delivery of dsRNA and vectors expressing such were not available (see for example Agami, R., page 833; Scherr et al. page 52, second column). As such, although Verma et al. and Anderson discuss issues of delivery and expression in reference to gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. RNA interference methods additionally have problems with transient inhibition effects (see for example Agami, R.). The specification provides methods of inhibition in plants, however the methods of delivery

of vectors in plants would not be feasible to apply in other organisms, particularly in mammals. Additionally, mammals have defense mechanisms that result in RNA degradation in vivo, as well as unpredictable immune responses precipitated by dsRNA, which do not occur in plants. The specification provides generic guidance with respect to delivery of vectors expressing double stranded RNA molecules to a cell in vivo (whole organism) for organisms other than plants, however, the specification does not provide specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of vectors to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid.

To practice the methods claimed, over the full scope claimed, it would require undue trial and error experimentation for the skilled artisan. Such experimentation would include the determination of how to specifically deliver a vector expressing a double stranded RNA to a target cell at a concentration effective enough to inhibit the expression of a target nucleic acid to the extent that a reduction in a phenotype is realized, the determination of an appropriate vector and enhancer-promoter combination for each target cell type "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response, how to prevent the transient inhibition of expression, and the determination of how to implement these methods in organisms other than plants.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance

by the inventor (beyond plants), the lack of working examples (for any organism besides plants), and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed, particularly in vivo for an organism other than a plant.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 6,506,559 (Fire et al.) is considered to be pertinent to Applicant's disclosure because it discloses methods of inhibiting the expression of a target gene using a dsRNA molecule, including an RNA molecule expressed from a DNA vector, however, Fire et al. does not teach these methods wherein the DNA vector comprises a heterologous intron, nor is there any suggestion in the prior art to include such an intron in the DNA vectors expressing a dsRNA of Fire et al.

Any rejection of record not repeated herein is considered to be withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
April 8, 2003

Karen A. Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER